Leal, I., Rodrigues, F. B., Sousa, D. C., Romão, V. C., Duarte, G. S., Carreño, E., Dick, A. D., Marques-Neves, C., Costa, J., & Fonseca, J. E. (2018). Efficacy and safety of intravitreal anti-tumour necrosis factor drugs in adults with non-infectious uveitis - a systematic review. *Acta Ophthalmologica*. https://doi.org/10.1111/aos.13699

1.Title Page

Title:

Efficacy and safety of intravitreal anti-TNF drugs in adults with non-infectious uveitis – a systematic review

Running head: Intravitreal anti-TNF drugs in adults with non-infectious uveitis – a systematic review

Authors

Inês Leal[1,2,3], Filipe B Rodrigues[4,5,6], David C Sousa[1,2,3], Vasco Crispim Romão[7,8], Gonçalo S Duarte[4,5], Ester Carreño[9], Andrew D. Dick[9,10,11], Carlos Marques-Neves[1,2,3], João Costa[4,5,12,13], João Eurico Fonseca[7,8]

Affiliations

[1] Department of Ophthalmology, Hospital de Santa Maria-CHLN, Lisbon Academic Medical Centre, PT

[2] Department of Ophthalmology, Faculdade de Medicina, Universidade de Lisboa,PT

[3] Centro de Estudos das Ciências da Visão, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

[4] Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

[5] Clinical Pharmacology Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

[6] Huntington's Disease Centre, University College London, London, UK

[7] Department of Rheumatology, Hospital de Santa Maria-CHLN, Lisbon Academic Medical Centre, PT

[8] Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

[9] Clinical Research Unit, Bristol Eye Hospital NHS Foundation Trust, Bristol, UK

[10] School of Clinical Sciences, Faculty of Medicine and Dentistry, University of Bristol, Bristol, UK

[11] National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK

[12] Evidence Based Medicine Centre, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

[13] Portuguese Collaborating Centre of the Cochrane Iberoamerican Network, Faculdade de Medicina, Universidade de Lisboa, Lisbon, PT

Corresponding author

João Eurico Fonseca

Rheumatology and Metabolic Bone Diseases Department,

Hospital de Santa Maria, CHLN,

Rheumatology Research Unit, Instituto de Medicina Molecular,

Faculty of Medicine, University of Lisbon,

Lisbon Academic Medical Centre, Portugal

Av. Professor Egas Moniz

1649-035 Lisboa, Portugal

jecfonseca@gmail.com

Telephone number: +351 217 805 252

Fax number: +351 217 805 653

2. Abstract

Purpose: Anti-tumor necrosis factor (TNF) drugs have been extensively used in non-infectious uveitis (NIU), when corticosteroids or conventional immunosuppressive drugs cannot adequately control inflammation or intolerable side effects accrue. However, systemic anti-TNF therapies are also associated with a myriad of side effects. Therefore, intravitreal administration of anti-TNF biologics has been employed to minimize patient morbidity and systemic adverse effects, while maintaining therapeutic effectivity. We undertook a systematic review to determine evidence of efficacy and safety of intravitreal administration of anti-TNF drugs in adults with NIU.

Methods: We conducted this systematic review according to the PRISMA guidelines. The protocol was registered with PROSPERO (CRD42016041946). We searched CENTRAL, MEDLINE and EMBASE, from inception to April 2017, as well as clinical trial registries and grey literature. The qualitative analysis included all studies of adult patients with a diagnosis of NIU and who received intravitreal anti-TNF drugs with a 4-week minimum follow-up.

Results: A total of 4840 references were considered for title and abstract screening. Seven full-texts were screened and five studies were considered for analysis. All studies were open-label, single-center, prospective, non-randomized, interventional case-series with a follow-up between 4 and 26 weeks, employing either adalimumab in two studies and infliximab in three. Three studies showed a treatment effect of anti-TNF intravitreal injections, while one study revealed short-term improvement and one study revealed no efficacy of anti-TNF intravitreal therapy. None of the studies reported ocular adverse effects but only two studies included electrophysiological assessment in the safety analysis and no study assessed systemic human anti-drug antibodies.

Conclusion: The available evidence is not sufficiently robust to conclude about the clinical effectivity of intravitreal anti-TNF in NIU and so no recommendation can be made. Intravitreal injection of anti-TNF antibodies remains a possible treatment option to be explored through robust clinical investigation.

Key-words: non-infectious uveitis, intravitreal, anti-tumor necrosis factor, biologics.

3. Text

Background

Uveitis comprises a heterogeneous group of intraocular inflammatory diseases. (Cordero-Coma & Sobrin 2015, Jabs 2005, Levy-Clarke et al. 2014) Non-infectious uveitis (NIU) are thought to result from an immune-mediated response to ocular antigens. Immune responses against ocular antigens in uveitis remain unknown, although retinal arrestin (also known as Soluble antigen or S-Ag) and interphotoreceptor retinoid binding protein (IRBP) have been proposed.(Mattapallil et al. 2011) Similarly, mechanisms of disease are not fully elucidated, in part because of the heterogeneity of uveitic conditions that we categorise under the umbrella term “NIU”. There is evidence that highlights the possibility that both autoinflammatory and autoimmune responses are operative in NIU. In particular, where activation of innate immune response leads to development of adaptive immune responses.(Janssen et al. 2012, Lee et al. 2014) Notwithstanding which pathways are at play, late complications of uveitis, such as cataract, glaucoma, or chronic macular edema can be sight threatening,(Androudi et al. 2010, Caspi 2010, Cordero-Coma & Sobrin 2015, Srivastava, Rajappa & Kaur 2010) and in developed countries, they represent one of the leading causes of blindness in the working age population. (Durrani et al. 2004) Substantial healthcare costs, workforce absence, leave of absence and long-term disability have been associated to NIU.(Thorne et al. 2016).

Overall, the goals of NIU therapy are to reduce ocular inflammation, avoid damage to anatomical structures, and prevent visual loss.(Cordero-Coma & Sobrin 2015, Levy-Clarke et al. 2014) Although corticosteroids have been the mainstay of therapy, they are often insufficient for adequate disease control, and are associated with numerous well-known systemic and local complications.(Lin, Suhler & Rosenbaum 2014, Pavesio et al. 2010, Sánchez-Cano et al. 2013) When inflammation is not well controlled by corticosteroids or side effects are unacceptable or intolerable, systemic immunomodulatory therapy (IMT) should be considered. Current IMT options comprise the biologics, such as monoclonal antibodies (mAb) and fusion proteins.(Giuliari, Sadaka & Hinkle 2014, Pasadhika & Rosenbaum 2014, Pavesio et al. 2010, Srivastava, Rajappa & Kaur 2010)

Different cytokines and chemokine have been involved in the pathogenesis of uveitis and have been shown to be elevated in patients with uveitis.(Carreño et al. 2016) Tumor necrosis factor (TNF) has been the leading target for NIU biologic treatment.(Caspi 2010, Cordero-Coma & Sobrin 2015, Dick et al. 2004, Nakamura et al. 1994, Srivastava, Rajappa & Kaur 2010) As a pleiotropic and multifunctional cytokine, TNF plays a pivotal role in ocular inflammation, via

reactive oxygen species, promotion of angiogenesis and breakdown of the blood-retinal barrier (BRB), being associated with the development of sight-threatening NIU-associated complications.(Caspi 2006, Caspi 2010, Cordero-Coma & Sobrin 2015, Levy-Clarke et al. 2014, Markomichelakis et al. 2012, Pulido et al. 2010, Shim 2011) Anti-TNF drugs have established efficacy in several systemic inflammatory conditions related to NIU such as Behçet disease(Hatemi et al. 2008), spondyloarthritis(Zochling et al. 2006), sarcoidosis(Maneiro et al. 2012) or juvenile idiopathic arthritis(Kalinina Ayuso et al. 2014, Ostring & Singh-Grewal 2013). The inactivation of TNF can been achieved with mAb, such as infliximab, adalimumab, golimumab, and certolizumab-pegol, or with receptor fusion proteins, as etanercept.(Cordero-Coma & Sobrin 2015, Levy-Clarke et al. 2014, Pulido et al. 2010) Currently these drugs are only approved for systemic administration and their route of administration and half-life are summarized on **Error! Reference source not found.** (adapted from Pascual-Camps, 2014).(Pascual-Camps et al. 2014)

Although these compounds are approved for other chronic immune-mediated inflammatory diseases and have shown positive results in the treatment of NIU (with variable levels of evidence and excluding etanercept), their use in NIU remains largely off-label, with the exception of adalimumab that was recently licenced after the publication of the VISUAL I and II trials.(Schwartzman 2016), (Jaffe et al. 2016, Levy-Clarke et al. 2014, Nguyen et al. 2016, Sánchez-Cano et al. 2013, Srivastava, Rajappa & Kaur 2010)

Several anti-TNF-related adverse effects have been described, such as reactivation of latent tuberculosis or hepatitis B virus, invasive fungal infections, central and peripheral neuropathies, and induction of immune disturbances.(Cordero-Coma & Sobrin 2015, Lawson, Thomas & Akobeng 2006, Levy-Clarke et al. 2014, Ma & Xu 2013, Pulido et al. 2010) Side effects related to systemic administration have led to the investigation of intravitreal route of administration, as an option that could curtail some of these unwanted effects while preserving therapeutic efficacy.(Levy-Clarke et al. 2014, Pascual-Camps et al. 2014) This route of drug delivery has been well established in uveitis treated with corticosteroids(Kane et al. 2008, Kempen et al. 2015, Reddy et al. 2016, Taylor et al. 2012), anti-vascular endothelial growth factor (VEGF),(Androudi et al. 2010, Tempest-Roe et al. 2013) or sirolimus.(Ibrahim et al. 2015, Vigil et al. 2015) In experimental autoimmune uveitis, intravitreal anti-TNF administration suppresses ocular inflammation particularly inhibiting macrophage activation that suppresses structural damage and prevents functional loss. Despite no direct effect in systemic cell migration to the eye, intravitreal anti-TNF has the opportunity and experimental evidence to curtail cell activation at the target site.(Khera et al. 2012) Nonetheless, in man, intravitreal administration of anti-TNF

is poorly studied, and contradictory results with respect to its efficacy and safety in NIU in both humans and animal models exist.(Androudi et al. 2010, Arevalo, Serrano & Wu 2013, Farvardin et al. 2010, Khalili et al. 2016, Markomichelakis et al. 2012, Pascual-Camps et al. 2014, Tempest-Roe et al. 2013)

The aim of this systematic review is to assess the efficacy and safety of intravitreal administration of anti-TNF drugs in adults with NIU, to discern opportunities and unmet needs.

Methods

Protocol and registration:

We conducted this systematic review and meta-analysis according to the PRISMA guidelines.(Liberati et al. 2009) The protocol was prospectively registered with PROSPERO (registration number: CRD42016041946) and done according to PRISMA-P guidelines.(Moher et al. 2015)

Eligibility criteria:

All studies, including case reports, case-series, cohorts, case-controls and clinical trials of adult patients – aged above 18 years old – with a clinical diagnosis of persistent NIU and where patients received intravitreal anti-TNF drugs with a minimum follow-up of 4 weeks. Persistent NIU is defined as inflammation of any part of the uvea (choroid, ciliary body and/or iris) that lasts for 3 or more months, after an infectious etiology has been excluded, or if there is a high suspicion of an immune-mediated underlying mechanism, which may occur isolated or in association with a systemic condition.(Jabs 2005) There were no restrictions regarding the number of participants reported in studies, year of and language of publication, publication status, or etiology of NIU.

Information sources:

For the identification of studies considered for inclusion in this review, detailed search strategies were developed for each database explored: Medline (from inception to April 2017), EMBASE (from inception to April 2017) and CENTRAL (from inception to April 2017). Grey literature was retrieved from appropriate databases from inception to April 2017 (www.opensigle.inist.fr; www.ntis.gov). Clinical trials registries (www.clinicaltrial.gov; www.clinicaltrialsregistry.eu) were also pursued from inception to April 2017. Non-English papers were equally assessed, translated as necessary and evaluated for inclusion. Reference lists were crosschecked, and whenever necessary, authors of published trials were contacted for further information and unpublished data.

Search:

The search strategy combined (uveitis) AND (etanercept OR infliximab OR adalimumab OR golimumab OR certolizumab). The search was restricted to humans. All terms were searched as free-text and as controlled vocabulary. The search strategies can be found in the Appendix 1.

Study selection:

Two independent review authors (DS, IL) assessed the references identified by the search strategy, read each of the titles and abstracts of the reports and selected for inclusion the appropriate ones. If there was no abstract, the report was retrieved in full text. Then, two review

authors (DS, IL) independently assessed the full-text articles for methodological quality and data extraction. Disagreements were resolved by discussion or by consensus with the participation of a third author (FBR).

Data collection process:

Two review authors (DS, IL) independently extracted the data onto standardized forms and crosschecked them for accuracy. Disagreements were resolved by discussion or reached by consensus with the participation of a third author (FBR).

Data synthesis

Due to the clinical and methodological heterogeneity of the available data, the studies retrieved were only qualitatively evaluated.

Results

Before de-duplication, a total of 5675 references were considered (MEDLINE 1582, Embase 4093, CENTRAL 93). Our grey literature strategy did not retrieve any reference. One reference was retrieved by hand-search.(Hamza et al. 2016) De-duplication generated 4840 references for screening. After title and abstract screening, seven studies were examined in full-text. Two studies were further excluded, one due to inappropriate study design (narrative review (Yeh et al. 2012)) and another due to wrong patient population (age-related macular degeneration (Giganti et al. 2010)). Five studies enrolling a total of 57 patients were thus included in the final analysis: one published in 2010 (Androudi et al. 2010), two published in 2012 (Farvardin, Afarid & Shahrzad 2012, Markomichelakis et al. 2012), one published in 2014 (Hamam et al. 2014) and one study published in 2016 (Hamza et al. 2016). We did not retrieve any unpublished studies. See Figure 1 for the Systematic review flow diagram.

Study characteristics

All studies were open-label, single-center, prospective, nonrandomized, interventional case-series. The number of participants in each study ranged from 7 to 20. Overall, the studies enrolled a total of 66 eyes from 57 patients, based on an intention-to-treat population. All studies evaluated intravitreal injection of anti-TNF in an open-label fashion. Table 1 summarizes individuals' studies characteristics regarding anti-TNF administered drug, dose, number and scheme of injections, and duration across studies. The main inclusion criteria were patients with active NIU in all but one study – Androudi, 2010, which included patients with controlled uveitis and persistent cystoid macular edema (CME) despite control of the inflammation. It is noteworthy that all studies bar two included patients with several etiologies of NIU. Markomichelakis, 2012 and Hamza, 2016 exclusively included patients with ocular inflammation associated with Behçet disease. Table 2 describes demographic characteristics of the enrolled subjects, uveitis etiologies, mean disease duration, possibility of concomitant conventional immunosuppressive treatment and number of patients naïve to anti-TNF drugs across studies. Across all studies, age ranged from 11 to 53 years-old and 32% (n=18) were female. All studies, except Farvardin, 2012, included adult patients only. Information about the lens status in each patient was provided only in Androudi, 2010. No study received industry funding.

The main outcome measures were: i) change in central macular thickness (CMT) on optical coherence tomography (OCT) in Androudi, 2010; ii) change in best-corrected visual acuity (BCVA) and change in CMT on OCT in Hamza, 2016; iii) change in the grade of inflammatory

anterior chamber cells and vitreous haze, change in fluorescein angiography (FA) score, change in CMT on OCT and change in electrophysiological tests in Hamam, 2014; iv) change in BCVA, change in the grade of inflammatory anterior chamber cells, vitreous haze and posterior segment in Markomichelakis, 2012; and v) change in BCVA, change in CMT on OCT, change in vitreous haze, number of patients with retinitis, vasculitis and papilitis and change in in electrophysiological tests in Hamza, 2016.

Tables 3 and 4 report results in each study regarding efficacy outcomes, namely number of patients with CME, mean OCT, mean CMT, mean BCVA, mean anterior chamber cells and mean vitreous haze at baseline and day 30 and the general authors' conclusion about the efficacy of the intervention.

CMT measured by OCT significantly decreased in Markomichelakis, 2012 and Farvardin, 2012 whereas this decrease was not significant in Androudi, 2010. In Hamam, 2014, only the change in median CMT between baseline and final visit (week 26) was reported, being statistically significant. About the OCT device used to assess the macula, 2 studies used a spectral-domain OCT device (Androudi, 2010 and Hamam, 2014), while the other three, used a time-domain OCT device. Regarding BCVA change, in Hamza, 2016, Markomichelakis, 2012 and Farvardin, 2012 there was a significant improvement, whereas in Androudi, 2010 it did not change significantly. In Hamam, 2014, it is impossible to draw a similar conclusion since BCVA was only reported at baseline and 26 weeks, (at 4 weeks was only the median and interquantile range are reported). Anterior chamber cells assessment according to the Standardization of Uveitis Nomenclature (SUN)(Jabs 2005) Working Group reporting is available in Markomichelakis, 2012 and Hamam, 2014 studies. In the former, a significant decrease in this parameter between baseline and week 4 is reported, whereas in Hamam, 2014, information about this parameter is only available at baseline and week 26th. The vitreous haze is reported in four studies. In Markomichelakis, 2012, Hamam, 2014 and Hamza, 2016 this grading was performed according to the SUN(Jabs 2005) , whereas in Farvardin, 2012 this grading was performed according to the BIO Score(Neri et al. 2013). In Markomichelakis, 2012, Hamza, 2016 and Farvardin, 2012, a significant vitreous haze difference was reported between baseline and week 4. In Hamam, 2014 study, the progression of the median of the vitreous haze was reported to decrease significantly after 26 weeks.

Regarding concurrent IMT, in Androudi, 2010 study, 4 patients were on oral IMT (with no further specification), one patient was not under nor had history of systemic IMT and 3 patients had a previous history of IMT (with no further specification); in Farvardin, 2012 study there is only mention to known absence of response to conventional IMT in the previous 3 months in all patients; in Hamam, 2014 study prior systemic IMT and results are detailed (patient 1 has received prior azathioprine and IFN-α-2a and had inflammation relapse, patient 2 has received prior cyclosporine A and discontinued 8 weeks after initiating intravitreal adalimumab, patient 3 had not received prior IMT and had documented inflammation relapse, patient 4 has received prior azathioprine and systemic adalimumab and had treatment failure, patient 5 has received prior azathioprine and had treatment failure, patient 6 has received prior methotrexate, IFN-α-2a and systemic with infliximab treatment failure and patient 7 received prior methotrexate, mycophenolate mofetil and azathioprine and was intolerant to conventional IMT; in Markomichelakis, 2012 study, 4 patients did not receive any prior IMT, 5 patients have received monotherapy with azathioprine or cyclosporine and 6 patients receiving combination therapy with azathioprine and cyclosporine. In this study, a sub-analysis was done to evaluate a possible influence of background IMT in these 3 subgroups of patients and statistical analysis did not reveal significant differences between the subgroups in all variables studied, including BCVA; finally in Hamza, 2016 study all patients received prior azathioprine and/or cyclophosphamide and did not suspend their background treatments when entering in the study.

Safety outcomes are detailed in Table 5. Systemic adverse effects were not reported in any study. Only in Androudi, 2010, 2 patients discontinued the study due to participants' preferences and one participant was lost to follow-up after the first injection. In the other four studies, there were no withdrawals independently of the reason. Only two studies reported electrophysiological assessment. No study assessed the development of anti-drug antibodies.

Taking the data together, three small observational studies (Hamam, 2014, Hamza, 2016 and Markomichelakis, 2012) showed a treatment effect of anti-TNF intravitreal injections in NIU when considering a variety of endpoints that were independently chosen for each study; one small observational study (Androudi, 2010) showed no efficacy of anti-TNF intravitreal injections, and one (Farvardin, 2012) found a short-term improvement in ocular inflammation with anti-TNF intravitreal injections. Finally, although a systematic review was performed according to PRISMA(Moher et al. 2015, The Prisma Group from Moher D, Liberati A, Tetzlaff J 2009) and Cochrane(Higgins & Green 2011) standards, we classified the level of evidence

found as 3a according to Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence(= et al. 2011) and no randomized controlled trials were retrieved in our search.

Discussion

Rationale for intravitreal administration of anti-TNF drugs

Anti-TNF drugs are widely used in several systemic immune-mediated conditions such as spondyloarthritis, rheumatoid arthritis and inflammatory bowel disease.(Markomichelakis et al. 2012) Specifically, adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF that blocks this molecule via an interaction with the p55 and p75 cell-surface TNF receptors.(Levy-Clarke et al. 2014, Neri et al. 2010, Neri et al. 2011) Infliximab is a monoclonal, chimeric (mouse/human) IgG1 κ antibody that binds to the soluble and transmembrane forms of TNF.(Cordero-Coma & Sobrin 2015, Suhler et al. 2005)

Firstly, the recently published VISUAL trials have provided level 1 evidence supporting the clinical efficacy of subcutaneous adalimumab in controlling inflammation and reducing the frequency of flares with a diverse range of uveitic diagnosis.(Jaffe et al. 2016, Nguyen et al. 2016) Although not formally approved for NIU, there are an important number of studies with infliximab specifically in two underlying conditions: Behçet disease and juvenile idiopathic arthritis.(Cordero-Coma & Sobrin 2015, Levy-Clarke et al. 2014) Moreover, evidence of the efficacy and safety of adalimumab and infliximab in adult NIU may also be found in case reports(Achille et al. 2016, Capote et al. 2014, Ermetcan et al. 2014, Leccese et al. 2011, Sakurai et al. 2016, Takase et al. 2011, Zmuda et al. 2013), retrospective case series(Al Rashidi et al. 2013, Alfawaz et al. 2014, Dobner et al. 2013, Durrani et al. 2016, Handa et al. 2011, Interlandi et al. 2014, Kim et al. 2016, Kruh et al. 2014, Mushtaq et al. 2007, Okada et al. 2012, Sobrin et al. 2007, Takeuchi et al. 2014, Vallet et al. 2016, van Denderen et al. 2014) and prospective case series.(Diaz-Llopis et al. 2008, Díaz-Llopis et al. 2012, Erckens et al. 2012, Joseph et al. 2003, Rudwaleit et al. 2009, Suhler et al. 2013, Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, Kurz PA, Lim L, Mackensen F, Pickard TD 2009)

Secondly, systemic TNF blockade can cause adverse events such as serious infections (notably tuberculosis reactivation), heart failure exacerbation and demyelinating disease.(Cordero-Coma & Sobrin 2015, Levy-Clarke et al. 2014, Nanau & Neuman 2014) Local treatment of uveitis remains useful, namely with steroids in both adult(Holbrook et al. 2015, Kane et al. 2008, Kempen et al. 2015, Lowder et al. 2011, Reddy et al. 2016, Tempest-Roe et al. 2013, Zarranz-Ventura et al. 2014) and pediatric uveitis.(Kempen et al. 2015, Sella et al. 2015, Taylor et al. 2012, Tomkins-Netzer et al. 2016) Thus, the possibility to administer these drugs directly into the eye may minimize systemic adverse effects of anti-TNF drugs, while achieving local therapeutic concentrations.(Androudi et al. 2010, Farvardin et al. 2010, Hamam et al. 2014, Markomichelakis et al. 2012) In support, intravitreal anti-TNF administration has been studied in

animal models with variable effects regarding efficacy and retinal toxicity.(Giansanti et al. 2008, Manzano et al. 2011, Melo et al. 2012, Theodossiadis et al. 2009, Tsilimbaris et al. 2009, Yuksel et al. 2014) The aim of the five studies included in our systematic review was to evaluate the safety and efficacy of intravitreal injections of anti-TNF drugs.

Although not fully understood, one pivotal purported mechanism in idiopathic NIU is activation and expansion of retinal antigen-specific CD4+ T lymphocytes and elaboration of non-specific innate immune responses.(Kerr et al. 2008, Khera et al. 2012, Lee et al. 2014) Also, high levels of the cytokine TNF in the aqueous humor of patients with NIU have been described in literature.(Kuiper et al. 2011, Sijssens et al. 2007) Thus, the inceptive rational for the intravitreal use of anti-TNF drugs is based on the efficacy of these drugs in NIU when used systemically(Durrani et al. 2016, Interlandi et al. 2014, Lin, Suhler & Rosenbaum 2014, Suhler et al. 2005, Vallet et al. 2016) and the capability to rapidly reach therapeutic drug levels in the eye when used intravitreally.(Modorati & Miserocchi 2012) One reason that may explain the lack of efficacy or long-term efficacy in some of the studies is that their mechanisms of action may not be effective when administered locally in the eye, given the systemic nature of the diseases underlying the inflammatory process.(Jaffe et al. 2016, Nguyen et al. 2016, Suhler et al. 2005, Tempest-Roe et al. 2013) Indeed, even in specific uveitic conditions with inflammation classically confined to the eye, such as birdshot chorioretinopathy, a systemic immune deviation has been shown.(Daien et al. 2017, Kuiper et al. 2011, Lee et al. 2014, Yang & Foster 2013) In the future, the combination of local and systemic anti-TNF therapy may be a reality to achieve optimal control of inflammation in NIU, alongside a more favorable safety profile.(Khera et al. 2012, Lee et al. 2014)

Summary of evidence

In four of the five included studies, although not long-lasting, a favorable outcome in terms of anatomy and function is reported. In Androudi, 2010 intravitreal adalimumab showed no efficacy in improving BCVA or decreasing CMT; however, it should be noted that in this particular study, all patients had refractory CME at baseline. Uveitic CME is thought to result from increased vascular permeability due to the breakdown of BRB and is a major risk factor for vision loss(Fardeau et al. 2015, Goldhardt & Rosen 2016) and often difficult to manage.(Androudi et al. 2010, Deuter et al. 2016, Fardeau et al. 2015, Goldhardt & Rosen 2016) As long standing CME will result in irreversible damage to as a result of outer retinal and photoreceptor damage, anatomical resolution of the CME will not lead to improvement in BCVA.(Androudi et al. 2010)

Notwithstanding this fact, in this study, the change in CMT with intravitreal adalimumab from baseline to the end of follow-up was not significant, a finding that may in part be explained by the small sample size.

In the five included studies there were no ocular adverse effects reported, although safety assessment was limited.

Safety Monitoring

With intravitreal administration, safety concerns have been raised by the experience of the use of anti-TNF in other ocular non-inflammatory conditions.(Yuksel et al. 2014) Specifically, infliximab injections may be both retinotoxic (documented with electrophysiology)(Giganti et al. 2010) and immunogenic.(Giganti et al. 2010, Wu et al. 2011) Only Hamza, 2016 and Hamam, 2014 included electrophysiological assessment, and their limited data showed that intravitreal infliximab and adalimumab, respectively, were not toxic. Another main concern with intravitreal anti-TNF is the potential immunogenicity, an adverse effect that has been reported in studies with intravitreal anti-TNF for non-uveitic conditions.(Arias et al. 2010, De Freitas et al. 2013, Giganti et al. 2010, Semeraro et al. 2013, Theodossiadis et al. 2009, Wu et al. 2011) None of the studies reported here demonstrated immunogenicity. However, in uveitic eyes an immunogenic reaction or change in pattern of the pre-existent inflammation is difficult to assess.(He et al. 2013) No study assessed systemic human anti-drug antibody responses. As such we are limited in concluding on the extent of immunogenicity following intravitreal administration in inflamed eyes.

Need for repeated injections

In Hamza, 2016 study, a need for repeated injection was inferred as a result because of deterioration in BCVA and increased vitreous haze between week 4 and 6. Markomichelakis, 2012 study recommends that repeated intravitreal versus intravenous administration of infliximab should be trialled.(Markomichelakis et al. 2012) Farvardin, 2012 proposes that the beneficial effect of intravitreal infliximab is not long lasting and, therefore, multiple injections may be required to achieve optimal inflammation control (Farvardin, Afarid & Shahrzad 2012), similarly to the current systemic treatment protocol with adalimumab or infliximab.(Jaffe et al. 2016, Jaffe et al. 2016, Mushtaq et al. 2007, Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, Kurz PA, Lim L, Mackensen F, Pickard TD 2009)

Limitations and unmet needs

Study designs were disparate across studies, namely regarding the anti-TNF drug used and the concentration and number of injections administered. Baseline population characteristics also presented differences, especially with respect to uveitis etiology. In addition, the OCT device used to image and measure CMT was different across studies contributing to differences that have been acknowledged regarding retinal thickness analysis and segmentation algorithms in the several studies.(Mylonas et al. 2009). The fact that concurrent/prior IMT is detailed only in 3 of 5 studies is a limitation in the interpretation these studies. We therefore emphasize the importance of specifically reporting these data, in order to draw more accurate conclusions of studies evaluating treatment outcomes in uveitis.

Finally, all studies had a small sample size. Further well-conducted and properly sized randomized controlled trials are needed to ascertain the effects of intravitreal anti-TNF drugs in NIU. Future studies should provide more robust and fast evidence of efficacy as well as determine intravitreal half-life and toxic effects.(Androudi et al. 2010) Following this step, and depending on the nature of the results, comparative, well-designed and adequately powered, randomized clinical trials should be sought. (Pulido et al. 2010)

Conclusions

Overall, the evidence is not sufficiently robust to conclude about the efficacy of intravitreal anti-TNF in chronic NIU (i.e., any estimate of the effect is very uncertain(Atkins et al. 2004)). The analyzed studies could not be directly compared or meta-analyzed due to fundamental heterogeneity in study design, inclusion criteria, doses and schema of drug administration, and endpoints. The authors conclude that no recommendation can be made and that intravitreal injection of anti-TNF antibodies remains a treatment possibility still to be adequately explored.

4. Acknowledgements

No acknowledgments.

5. References:

= OT of EWG, Howick J, Chalmers I (James LL, et al. (2011): The Oxford 2011 Levels of Evidence. Oxford Cent Evidence-Based Med.

Achille M, Ilaria P, Teresa G, Roberto C, Ilir A, Piergiorgio N, Rolando C & Gabriele S (2016): Successful treatment with adalimumab for severe multifocal choroiditis and panuveitis in presumed (early-onset) ocular sarcoidosis. Int Ophthalmol **36**: 129–135.

Al Rashidi S, Al Fawaz A, Kangave D & Abu El-Asrar AM (2013): Long-term Clinical Outcomes in Patients with Refractory Uveitis Associated with Behçet Disease Treated with Infliximab. Ocul Immunol Inflamm **21**: 1–7.

Alfawaz A, Alrashidi S, Kalantan H, Al-Mezaine H & Abu El-Asrar AM (2014): Cataract surgery under systemic infliximab therapy in patients with refractory uveitis associated with Behcet disease. Ann Saudi Med **34**: 328–333.

Androudi S, Tsironi E, Kalogeropoulos C, Theodoridou A & Brazitikos P (2010): Intravitreal adalimumab for refractory uveitis-related macular edema. Ophthalmology **117**: 1612–1616.

Androudi S, Tsironi E, Kalogeropoulos C, Theodoridou A & Brazitikos P (2010): Intravitreal adalimumab for refractory uveitis-related macular edema. Ophthalmology **117**: 1612–1616.

Arevalo JF, Serrano M a & Wu L (2013): Combined inhibition of tumor necrosis factor (TNF) and vascular endothelial growth factor (VEGF) for the treatment of macular edema of various etiologies: a short-term pilot study. Eye **27**: 569–571.

Arias L, Caminal JM, Badia MB, Rubio MJ, Catala J & Pujol O (2010): Intravitreal infliximab in patients with macular degeneration who are nonresponders to antivascular endothelial growth factor therapy. Retina **30**: 1601–1608.

Atkins D, Best D, Briss P a, et al. (2004): Grading quality of evidence and strength of recommendations. Br Med J **328**: 1490.

Capote A, Jiménez J, Soto M, Gómez C & Lucas M (2014): Effectiveness of Adalimumab for Refractory Serpiginous Choroiditis. Ocul Immunol Inflamm **22**:.

Carreño E, Portero A, Herreras JM, García-Vázquez C, Whitcup SM, Stern ME, Calonge M & Enríquez-de-Salamanca A (2016): Cytokine and chemokine tear levels in patients with uveitis. Acta Ophthalmol 1–10.

Caspi RR (2006): Animal models of autoimmune and immune-mediated uveitis. Drug Discov Today Dis Model **3**: 3–9.

Caspi RR (2010): A look at autoimmunity and inflammation in the eye. J Clin Invest **120**: 3073–3083.

Cordero-Coma M & Sobrin L (2015): Anti-Tumor Necrosis Factor-α Therapy in Uveitis. Surv Ophthalmol.

Daien V, Mura F, Martin G, et al. (2017): Th17 and regulatory T cells are increased in blood of patients with birdshot chorioretinopathy. Acta Ophthalmol **95**: e161–e163.

De Freitas LGA, Isaac DLC, Tannure WT, Gabriel LAR, Dos Reis RG, Rassi AR, De Freitas CA & De Ávila MP (2013): Intravitreal bevacizumab combined with infliximab in the treatment of choroidal neovascularization secondary to age-related macular degeneration: Case report series. Arq Bras Oftalmol **76**: 180–184.

Deuter CME, Zierhut M, Igney-Oertel A, Xenitidis T, Feidt A, Sobolewska B, Stuebiger N & Doycheva D (2016): Tocilizumab in Uveitic Macular Edema Refractory to Previous Immunomodulatory Treatment. Ocul Immunol Inflamm **3948**: 1–6.

Diaz-Llopis M, García-Delpech S, Salom D, Udaondo P, Hernández-Garfella M, Bosch-Morell F, Quijada A & Romero FJ (2008): Adalimumab therapy for refractory uveitis: a pilot study. J Ocul Pharmacol Ther **24**: 351–61.

Díaz-Llopis M, Salom D, Garcia-De-Vicuña C, et al. (2012): Treatment of refractory uveitis with adalimumab: A prospective multicenter study of 131 patients. Ophthalmology **119**: 1575–1581.

Dick AD, Forrester J V, Liversidge J & Cope AP (2004): The role of tumour necrosis factor

(TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res **23**: 617–37.
Dobner BC, Max R, Becker MD, Heinz C, Veltrup I, Heiligenhaus A, Barisani-Asenbauer T & Mackensen F (2013): A three-centre experience with adalimumab for the treatment of non-infectious uveitis. Br J Ophthalmol **97**: 134–8.
Durrani K, Kempen JH, Ying GS, et al. (2016): Adalimumab for Ocular Inflammation. Ocul Immunol Inflamm 1–8.
Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P & Murray PI (2004): Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol **88**: 1159–1162.
Erckens RJ, Mostard RLM, Wijnen PAHM, Schouten JS & Drent M (2012): Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefe's Arch Clin Exp Ophthalmol **250**: 713–720.
Ermetcan A, Emre S, Ozturk F, Gençoglan G & Gunduz K (2014): Psoriatic uveitis responding to adalimumab therapy. Int J Dermatol **Apr;53**: 271–3.
Fardeau C, Champion E, Massamba N & LeHoang P (2015): [Uveitic macular edema]. J Fr Ophtalmol **38**: 74–81.
Farvardin M, Afarid M, Mehryar M & Hosseini H (2010): Intravitreal infliximab for the treatment of sight-threatening chronic noninfectious uveitis. Retina **30**: 1530–1535.
Farvardin M, Afarid M & Shahrzad S (2012): Long-Term Effects of Intravitreal Infliximab for Treatment of Sight Threatening Chronic Noninfectious Uveitis. J Ocul Pharmacol Ther **28**: 120906061906007.
Giansanti F, Ramazzotti M, Vannozzi L, et al. (2008): A pilot study on ocular safety of intravitreal infliximab in a rabbit model. Investig Ophthalmol Vis Sci **49**: 1151–1156.
Giganti M, Beer PM, Lemanski N, Hartman C, Schartman J & Falk N (2010): Adverse events after intravitreal infliximab (Remicade). Retina **30**: 71–80.
Giuliari GP, Sadaka A & Hinkle DM (2014): Biologic agents in experimental autoimmune uveitis. Int Ophthalmol **34**: 145–156.
Goldhardt R & Rosen BS (2016): Uveitic Macular Edema: Treatment Update. Curr Ophthalmol Rep **4**: 30–37.
Hamam RN, Barikian AW, Antonios RS, Abdulaal MR, Alameddine RM, El Mollayess G & Mansour AM (2014): Intravitreal Adalimumab in Active Noninfectious Uveitis: A Pilot Study. Ocul Immunol Inflamm **24**: 319–26.
Hamza MME, Macky TA, Frcse D & Sidky MK (2016): INTRAVITREAL INFLIXIMAB IN REFRACTORY UVEITIS IN BEHCET ' S DISEASE A Safety and Efficacy Clinical Study. Retina **36**: 2399–2408.
Handa T, Tsunekawa H, Yoneda M, Watanabe D, Mukai T, Yamamura M, Iwaki M & Zako M (2011): Long-term remission of ocular and extraocular manifestations in Beh??et's disease using infliximab. Clin Exp Rheumatol **29**:.
Hatemi G, Silman a, Bang D, et al. (2008): EULAR recommendations for the management of Behçet disease. Ann Rheum Dis **67**: 1656–62.
He Q, Johnston J, Zeitlinger J, et al. (2013): Update on intravitreal anti-tumor necrosis factor alpha therapies for ocular disorders. Econ Bot **33**: 395–401.
Higgins J & Green S (2011): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.
Holbrook JT, Sugar EA, Burke AE, et al. (2015): Dissociations of the Fluocinolone Acetonide Implant: The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study. Am J Ophthalmol 29–36.
Ibrahim MA, Sepah YJ, Watters A, Bittencourt M, Vigil EM, Do D V. & Nguyen QD (2015): One-Year Outcomes of the SAVE Study: Sirolimus as a Therapeutic Approach for UVEitis. Transl Vis Sci Technol **4**:.
Interlandi E, Leccese P, Olivieri I & Latanza L (2014): Adalimumab for treatment of severe

Behcet's uveitis: a retrospective long-term follow-up study. Clin Exp Rheumatol **32**: S58-62.
Jabs DA (2005): Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol **140**: 509–516.
Jaffe GJ, Dick AD, Brézin AP, et al. (2016): Adalimumab in Patients with Active Noninfectious Uveitis. N Engl J Med **375**: 932–943.
Jaffe GJ, Dick AD, Brézin AP, et al. (2016): Adalimumab in patients with active noninfectious uveitis. N Engl J Med **275**: Supplementary Appendix.
Janssen CEI, Rose CD, De Hertogh G, et al. (2012): Morphologic and immunohistochemical characterization of granulomas in the nucleotide oligomerization domain 2-related disorders Blau syndrome and Crohn disease. J Allergy Clin Immunol **129**: 1076–1084.
Joseph A, Raj D, Dua HS, Powell PT, Lanyon PC & Powell RJ (2003): Infliximab in the treatment of refractory posterior uveitis. Ophthalmology **110**: 1449–1453.
Kalinina Ayuso V, Makhotkina N, van Tent-Hoeve M, de Groot-Mijnes JDF, Wulffraat NM, Rothova A & de Boer JH (2014): Pathogenesis of juvenile idiopathic arthritis associated uveitis: The known and unknown. Surv Ophthalmol **59**: 517–531.
Kane FE, Burdan J, Cutino A & Green KE (2008): Iluvien: a new sustained delivery technology for posterior eye disease. Expert Opin Drug Deliv **5**: 1039–1046.
Kempen JH, Altaweel MM, Drye LT, Holbrook JT, Jabs DA, Sugar EA, Thorne JE & Group TMUST (MUST) TFSR (2015): Benefits of Systemic Anti-inflammatory Therapy versus Fluocinolone Acetonide Intraocular Implant for Intermediate Uveitis, Posterior Uveitis, and Panuveitis: Fifty-four-Month Results of the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up . Ophthalmology **122**: 1967–75.
Kempen JH, Altaweel MM, Drye LT, Holbrook JT, Jabs DA, Sugar EA, Thorne JE & Group TMUST (MUST) TFSR (2015): Quality of Life and Risks Associated with Systemic Anti-inflammatory Therapy Versus Fluocinolone Acetonide Intraocular Implant for Intermediate, Posterior or Panuveitis: 54 month results of The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow. Ophthalmology **122**: 1976–1986.
Kerr EC, Copland DA, Dick AD & Nicholson LB (2008): The dynamics of leukocyte infiltration in experimental autoimmune uveoretinitis. Prog Retin Eye Res **27**: 527–535.
Khalili H, Lee RW, Khaw PT, Brocchini S, Dick AD & Copland DA (2016): An anti-TNF-α antibody mimetic to treat ocular inflammation. Sci Rep **6**: 36905.
Khera TK, Copland DA, Boldison J, Lait PJP, Szymkowski DE, Dick AD & Nicholson LB (2012): Tumour necrosis factor-mediated macrophage activation in the target organ is critical for clinical manifestation of uveitis. Clin Exp Immunol **168**: 165–177.
Kim M, Won J-Y, Choi SY, Ju JH & Park Y-H (2016): Anti-TNFα treatment for HLA-B27 positive ankylosing spondylitis-related uveitis. Am J Ophthalmol **170**: 32–40.
Kruh JN, Yang P, Suelves AM & Foster CS (2014): Infliximab for the treatment of refractory noninfectious uveitis: A study of 88 patients with long-term follow-up. Ophthalmology **121**: 358–364.
Kuiper JJW, Mutis T, De Jager W, De Groot-Mijnes JDF & Rothova A (2011): Intraocular interleukin-17 and proinflammatory cytokines in HLA-A-29-associated birdshot chorioretinopathy. Am J Ophthalmol **152**:.
Lawson M, Thomas A & Akobeng A (2006): Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis (Review). Cochrane Database Syst Rev 1–29.
Leccese P, Latanza L, D'Angelo S, A P & Olivieri I (2011): Efficacy of switching to adalimumab in a patient with refractory uveitis of Behçet's disease to infliximab. Clin Exp Rheumatol **Jul-Aug;29**: S93.
Lee RW, Nicholson LB, Sen HN, Chan C-C, Wei L, Nussenblatt RB & Dick AD (2014): Autoimmune and autoinflammatory mechanisms in uveitis. Semin Immunopathol **36**: 581–94.
Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A & Van Gelder RN (2014): Expert

panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology **121**: 785–796.
Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A & Van Gelder RN (2014): Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders. Ophthalmology **121**: 785–796.e3.
Liberati A, Altman DG, Tetzlaff J, et al. (2009): Annals of Internal Medicine Academia and Clinic The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions : Ann Intern Med **151**: W65–W94.
Lin P, Suhler EB & Rosenbaum JT (2014): The future of uveitis treatment. Ophthalmology **121**: 365–376.
Lowder C, Belfort R, Lightman S, et al. (2011): Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol **129**: 545–53.
Ma X & Xu S (2013): TNF inhibitor therapy for rheumatoid arthritis (Review). Biomed Reports **1**: 177–184.
Maneiro JR, Salgado E, Gomez-Reino JJ & Carmona L (2012): Efficacy and Safety of TNF Antagonists in Sarcoidosis: Data from the Spanish Registry of Biologics BIOBADASER and a Systematic Review. Semin Arthritis Rheum **42**: 89–103.
Manzano RP a, Peyman G a, Carvounis PE, et al. (2011): Toxicity of high-dose intravitreal adalimumab (Humira) in the rabbit. J Ocul Pharmacol Ther **27**: 327–331.
Markomichelakis N, Delicha E, Masselos S & Sfikakis PP (2012): Intravitreal infliximab for sight-threatening relapsing uveitis in Beh??et disease: A pilot study in 15 patients. Am J Ophthalmol **154**: 534–541.e1.
Mattapallil MJ, Silver PB, Mattapallil JJ, et al. (2011): Uveitis-associated epitopes of retinal antigens are pathogenic in the humanized mouse model of uveitis and identify autoaggressive T cells. J Immunol **187**: 1977–1985.
Melo GB, Moraes Filho MN, Rodrigues EB, et al. (2012): Toxicity and Retinal Penetration of Infliximab in Primates. Retina **32**: 606–612.
Modorati G & Miserocchi E (2012): Intravitreal injection therapy in the treatment of noninfectious uveitis. Dev Ophthalmol **51**: 110–121.
Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P & Stewart LA (2015): Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev **4**: 1.
Mushtaq B, Saeed T, Situnayake RD & Murray PI (2007): Adalimumab for sight-threatening uveitis in Behçet's disease. Eye (Lond) **21**: 824–825.
Mylonas G, Ahlers C, Malamos P, Golbaz I, Deak G, Schuetze C, Sacu S & Schmidt-Erfurth U (2009): Comparison of retinal thickness measurements and segmentation performance of four different spectral and time domain OCT devices in neovascular age-related macular degeneration. Br J Ophthalmol **93**: 1453–60.
Nakamura S, Yamakawa T, Sugita M, Kijima M, Ishioka M, Tanaka S & Ohno S (1994): The role of tumor necrosis factor-alpha in the induction of experimental autoimmune uveoretinitis in mice. Invest Ophthalmol Vis Sci **35**: 3884–3889.
Nanau RM & Neuman MG (2014): Safety of anti-tumor necrosis factor therapies in arthritis patients. J Pharm Pharm Sci **17**: 324–61.
Neri P, Capuano V, Pirani V, Arapi I, Mariotti C & Giovannini A (2013): Signs and symptoms of uveitis. Acta Ophthalmol **91**:.
Neri P, Lettieri M, Fortuna C, Zucchi M, Manoni M, Celani S & Giovannini A (2010): Adalimumab (humira™) in ophthalmology: a review of the literature. Middle East Afr J Ophthalmol **17**: 290–296.
Neri P, Zucchi M, Allegri P, Lettieri M, Mariotti C & Giovannini A (2011): Adalimumab (Humira™): A promising monoclonal anti-tumor necrosis factor alpha in ophthalmology. Int Ophthalmol. 165–173.

Nguyen QD, Merrill PT, Jaffe GJ, et al. (2016): Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet (London, England) **6736**: 1–10.
Nguyen QD, Merrill PT, Jaffe GJ, et al. (2016): Adalimumab for prevention of uveitic flarein patients with inactive non-infectious uveitic controlled by corticosteroids (VISUAL II): a multicentre, double masked, randomised, placebo-controlled phase 3 trial. Lancet (London, England) **275**:.
Okada A a, Goto H, Ohno S, Mochizuki M & Japan OBDRGO (2012): Multicenter study of infliximab for refractory uveoretinitis in Behcet disease. Arch Ophthalmol **130**: 592–598.
Ostring GT & Singh-Grewal D (2013): Juvenile idiopathic arthritis in the new world of biologics. J Paediatr Child Heal **49**: E405-12.
Pasadhika S & Rosenbaum JT (2014): Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics **8**: 67–81.
Pascual-Camps I, Hernández-Martínez P, Monje-Fernández L, Dolz-Marco R, Gallego-Pinazo R, Wu L, Arévalo JF & Díaz-Llopis M (2014): Update on intravitreal anti-tumor necrosis factor alpha therapies for ocular disorders. Econ Bot **4**: 1–5.
Pavesio C, Zierhut M, Bairi K, Comstock TL & Usner DW (2010): Evaluation of an Intravitreal Fluocinolone Acetonide Implant versus Standard Systemic Therapy in Noninfectious Posterior Uveitis. Ophthalmology **117**: 567–575.e1.
Pulido JS, Pulido ES, Michet CJ & Vile RG (2010): More Questions Than Answers: A Call for a Moratorium on the Use of Intravitreal Infliximab Outside of a Well-Designed Trial. Retina **30**: 1–5.
Reddy AK, Burkholder BM, Khan IR & Thorne JE (2016): Iluvien Implantation for Uveitis and Uveitic Macular Edema. Ocul Immunol Inflamm **0**: 1–2.
Rudwaleit M, Rødevand E, Holck P, Vanhoof J, Kron M, Kary S & Kupper H (2009): Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis **68**: 696–701.
Sakurai Y, Namba K, Mizuuchi K, Nomura T & Ishida S (2016): A Case of Severe Panuveitis Associated with Psoriasis Vulgaris Successfully Treated with Infliximab. Case Rep Ophthalmol **7**: 191–194.
Sánchez-Cano D, Callejas-Rubio JL, Ruiz-Villaverde R, Ríos-Fernández R & Ortego-Centeno N (2013): Off-label uses of anti-TNF therapy in three frequent disorders: Behçet's disease, sarcoidosis, and noninfectious uveitis. Mediators Inflamm **2013**: 286857.
Schwartzman S (2016): Advancements in the management of uveitis. Best Pract Res Clin Rheumatol **30**: 304–315.
Sella R, Oray M, Friling R, Umar L, Tugal-Tutkun I & Kramer M (2015): Dexamethasone intravitreal implant (Ozurdex??) for pediatric uveitis. Graefe's Arch Clin Exp Ophthalmol **253**: 1777–1782.
Semeraro F, Romano MR, Danzi P, Angi M & Costagliola C (2013): Intravitreal infliximab for choroidal neovascularization in patients refractory to conventional treatments. Int J Immunopathol Pharmacol **26**: 765–768.
Shim H (2011): One target, different effects: a comparison of distinct therapeutic antibodies against the same targets. Exp Mol Med **43**: 539.
Sijssens KM, Rijkers GT, Rothova A, Stilma JS, Schellekens PAWJF & de Boer JH (2007): Cytokines, chemokines and soluble adhesion molecules in aqueous humor of children with uveitis. Exp Eye Res **85**: 443–449.
Sobrin L, Kim EC, Christen W, Papadaki T, Letko E & Foster CS (2007): Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol **125**: 895–900.
Srivastava A, Rajappa M & Kaur J (2010): Uveitis: Mechanisms and recent advances in therapy.

Clin Chim Acta **411**: 1165–1171.
Suhler EB, Lowder CY, Goldstein D a, et al. (2013): Adalimumab therapy for refractory uveitis: results of a multicentre, open-label, prospective trial. Br J Ophthalmol **97**: 481–6.
Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD & Rosenbaum JT (2005): A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol **123**: 903–12.
Suhler EB, Smith JR, Giles TR, Lauer AK, Wertheim MS, Kurz DE, Kurz PA, Lim L, Mackensen F, Pickard TD RJ (2009): Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Br J Ophthalmol **127**: 819–22.
Takase K, Ohno S, Ideguchi H, Uchio E, Takeno M & Ishigatsubo Y (2011): Successful switching to adalimumab in an infliximab-allergic patient with severe Beh??et disease-related uveitis. Rheumatol Int **31**: 243–245.
Takeuchi M, Kezuka T, Sugita S, et al. (2014): Evaluation of the long-term efficacy and safety of infliximab treatment for uveitis in Behçet's disease: A multicenter study. Ophthalmology **121**: 1877–1884.
Taylor SRJ, Tomkins-Netzer O, Joshi L, Morarji J, McLoone E & Lightman S (2012): Dexamethasone implant in pediatric uveitis. Ophthalmology **119**: 2010–2012.
Tempest-Roe S, Joshi L, Dick AD & Taylor SRJ (2013): Local therapies for inflammatory eye disease in translation: past, present and future. BMC Ophthalmol **13**: 39.
Tempest-Roe S, Joshi L, Dick AD & Taylor SRJ (2013): Local therapies for inflammatory eye disease in translation: past, present and future. BMC Ophthalmol **13**: 39.
The Prisma Group from Moher D, Liberati A, Tetzlaff J AD (2009): Preferred reporting items for systematic reviews and meta analyses: The Prisma Statement. PLoS Med **6**: 1–15.
Theodossiadis PG, Liarakos VS, Sfikakis PP, Charonis A, Agrogiannis G, Kavantzas N & Vergados IA (2009): Intravitreal administration of the anti-TNF monoclonal antibody Infliximab in the rabbit. Graefe's Arch Clin Exp Ophthalmol **247**: 273–281.
Thorne JE, Skup M, Tundia N, Macaulay D, Revol C, Chao J, Joshi A & Dick AD (2016): Direct and indirect resource use, healthcare costs and work force absence in patients with non-infectious intermediate, posterior or panuveitis. Acta Ophthalmol **94**: e331–e339.
Tomkins-Netzer O, Talat L, Seguin-Greenstein S, Bar A & Lightman S (2016): Outcome of Treating Pediatric Uveitis with Dexamethasone Implants. Am J Ophthalmol **161**: 110–115e2.
Tsilimbaris M, Diakonis VF, Naoumidi I, Charisis S, Kritikos I, Chatzithanasis G, Papadaki T & Plainis S (2009): Evaluation of potential retinal toxicity of adalimumab (Humira). Graefe's Arch Clin Exp Ophthalmol **247**: 1119–1125.
Vallet H, Seve P, Biard L, et al. (2016): Infliximab Versus Adalimumab in the Treatment of Refractory Inflammatory Uveitis: A Multicenter Study from the French Uveitis Network. Arthritis Rheumatol **68**: 1522–1530.
van Denderen JC, Visman IM, Nurmohamed MT, Suttorp-Schulten MS a & van der Horst-Bruinsma IE (2014): Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with ankylosing spondylitis. J Rheumatol **41**: 1843–8.
Vigil E, Sepah Y, Watters A, et al. (2015): Assessment of changes in quality of life among patients in the SAVE Study - Sirolimus as therapeutic Approach to uVEitis: a randomized study to assess the safety and bioactivity of intravitreal and subconjunctival injections of sirolimus in patients with . J Ophthalmic Inflamm Infect **Apr 18**: eCollection 2015.
Wu L, Hernandez-Bogantes E, Roca J a, Arevalo JF, Barraza K & Lasave AF (2011): intravitreal tumor necrosis factor inhibitors in the treatment of refractory diabetic macular edema: a pilot study from the Pan-American Collaborative Retina Study Group. Retina **31**: 298–303.
Yang P & Foster CS (2013): Interleukin 21, interleukin 23, and transforming growth factor ??1 in HLA-A29-associated birdshot retinochoroidopathy. Am J Ophthalmol **156**:.
Yeh S, Albini TA, Moshfeghi AA & Nussenblatt RB (2012): Uveitis, the comparison of age-

related macular degeneration treatments trials (CATT), and intravitreal biologics for ocular inflammation. Am J Ophthalmol.

Yuksel E, Hasanreisoglu B, Yuksel N, Yilmaz G, Ercin U & Bilgihan A (2014): Comparison of Acute Effect of Systemic Versus Intravitreal Infliximab Treatment in an Experimental Model of Endotoxin-Induced Uveitis. J Ocul Pharmacol Ther **30**: 74–80.

Zarranz-Ventura J, Carreño E, Johnston RL, et al. (2014): Multicenter study of intravitreal dexamethasone implant in noninfectious uveitis: Indications, outcomes, and reinjection frequency. Am J Ophthalmol **158**: 1136–1145.e5.

Zmuda M, Tiev KP, Knoeri J & Héron E (2013): Successful use of infliximab therapy in sight-threatening corticosteroid-resistant Vogt-Koyanagi-Harada disease. Ocul Immunol Inflamm **21**: 310–6.

Zochling J, van der Heijde D, Burgos-Vargas R, et al. (2006): ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis **65**: 442–52.

6. Figure and figure legends

None

7. Tables

Table 1 Summary of the route of administration and half-life of the commercial available monoclonal TNF inhibitors (adapted from Pascual-Camps, 2014).(Pascual-Camps et al. 2014)

Generic name	Route of administration	Half-life (days)
Adalimumab	Subcutaneous injection	14
Certolizumab		14
Etanercept		4 to 6
Golimumab		14
Infliximab	Intravenous infusion	8 to 10

Table 2 General features by study

Study	Type of study	Number of patients/eyes	Anti-TNF drug	Dose	Number of injections	Study duration
Androudi S, 2010	Open-label, single-center, prospective, nonrandomized, interventional case series	8/8 (but results data only about 5 patients due to withdrawals)	ADA	0.5 mg/ 0.05 mL and reinjection with an escalating dose of 1 mg/0.05 ml	Three: baseline, 1 month and 2 months and reinjection, with an escalating dose of 1 mg/0.05 ml performed if at least 1 of the following retreatment criteria were met during the follow-up examination: 1) decrease in BCVA by >= 5 letters compared with previous visit; 2) increase in foveal retinal thickness by >=100 microns compared with previous visit OCT values	6 months
Farvardin M, 2012		7/10	IFX	1.5 mg/0.15 mL	Single injection	6 months
Haman RN, 2014		7/13	ADA	1.5 mg/0.03 mL with possible higher dose of subsequent injections (2.5 mg/0.05 mL)	Injection at baseline, 2 weeks and then monthly for a total of 7 injections. Patients with deterioration of BCVA of two or more lines or worsening of inflammation by at least 2+ cell/haze at any time during follow-up were withdrawn; Patients with no or minimal improvement (<2+ cells/haze, fluorescein leakage and vascular staining) and stable ERG received a higher dose of subsequent injections (2.5 mg/0.05 mL)	26 weeks
Markomichelakis N, 2012		15/15	IFX	1 mg/ 0.05 mL	Single injection	4 weeks
Hamza MME, 2016		20/20	IFX	1 mg/0.05 mL	Three consecutive intravitreal injections 6 weeks apart	18 weeks

Legend: TNF: tumor necrosis factor; ADA: adalimumab; IFX: infliximab; BCVA: best corrected-visual acuity; OCT optical coherence tomography; ERG: electroretinogram

Table 3 Demographic characteristics of subjects enrolled in all studies

Study	Female gender n(%)	Age in years mean ± SD (range)	Inclusion criteria	Mean disease duration	Concomitant conventional immunosuppression	Naïve to anti-TNF drugs
Androudi S, 2010	4 (50.0)	37 ± 0 (23-52)	Patients with CME, despite control of their ocular inflammation, who had failed previous CME therapies	NS	Yes, not all patients	NS
Farvardin M, 2012	6 (85.7)	26.6 ±12.8 (11-50)	Behçet (4), JIA (1), multifocal choroiditis and panuveitis (1), pars planitis (1) with no response to conventional treatments in the previous 3 months	NS	NS	NS
Haman RN, 2014	2 (28.6)	37.5 (19-48)	Behçet uveitis (4 patients) and idiopathic (3 patients)	48 (4-96) months	Yes, not all patients	5 patients (2 had had ADA or IFX)
Markomichelakis N, 2012	5 (33.3)	35.3 ± 8.9 (23-53)	Relapsing ocular inflammation associated with Behçet disease with unilateral sight-threatening posterior segment flare	5.6 ± 4.3 years	Yes	13
Hamza MME, 2016	1 (5.0)	31.4 ± 3.5 (26-38)	Refractory posterior uveitis in Behçet's disease	NS	Yes	20 (only previous conventional immunosuppression was allowed)

Legend: CI: confidence interval; CME: cystoids macular edema; JIA: juvenile idiopathic arthritis; NS: not stated; TNF: tumor necrosis factor; TNFi: tumor necrosis factor inhibitor; ADA: adalimumab; IFX: infliximab

Table 4 Efficacy outcomes across studies I

Study	Cystoid macular edema at baseline (number of patients)	Cystoid macular edema at day 30 (number of patients)	Significance of change (p-value)	OCT CMT at baseline (µm) mean ± SD (range)	OCT CMT at day 30 (µm) mean ± SD (range)	Significance of change (p-value)	BCVA baseline (logMar) mean ± SD (range)	BCVA day 30 (logMar) mean ± SD (range)	Significance of change (p-value)
Androudi S, 2010	8 in 8	8 in 8	Non-significant	692	611	Non-significant	1.1*	1.0*	Non-significant
Farvardin M, 2012	NS		-	673.2 ± 338.39	456.4 ± 317.46	0.01	1.37 ± 0.14 (1 to 2.07)	0.68 ± 0.56 (0.3 to 1.78)	<0.001
Haman RN, 2014	8 in 13	NS	-	320 (170 to 512)	NS	-	0.53*	NS	-
Markomichelakis N, 2012	11 in 15	9 in 15	Non-significant	434 (364 to 504)	309 (227 to 391)	< 0.001	0.74 (0.51 to 0.96)	0.30 (0.07to 0.52)	< 0.0001
Hamza MME, 2016	NS		-	361	239	< 0.0001	0.94 ± 0.32	0.41± 0.18	< 0.0001

Legend: NS: not-stated; OCT: optical coherence tomography; CMT: central macular thickness; BCVA: best-corrected visual acuity; * after conversion to LogMar

Table 2 Efficacy outcomes across studies II

Study	Mean anterior chamber cells (95% CI) baseline (range)	Mean anterior chamber cells (95% CI) day 30 (range)	Significance of change (p value)	Mean vitreous haze (95% CI) baseline	Mean vitreous haze (95% CI) day 30	Significance of change (p value)	Intravitreal anti-TNF treatment considered efficacious ?
Androudi S, 2010	NS	NS	-	NS	NS	-	No
Farvardin M, 2012	NS	NS	-	2.7±0.82	0.95±0.43	< 0.0005	Yes, but temporary effect
Haman RN, 2014	0.62 (range: 0-4)	NS	-	1,19 (0-3)	NS	-	Yes
Markomichelakis N, 2012	2.13 (1.55-2.72)	0.20 (0.0-0.51)	< 0.0001	1.73 (1.24-2.22)	0.33 (0.06-0.60)	< 0.0001	Yes
Hamza MME, 2016	NS	NS	-	2	0.2	< 0.0001	Yes, but probable temporary effect

Legend: CI: confidence interval; NS: non-significant; TNF: tumor necrosis factor

Table 6 Safety outcomes across studies

Study	Anti-TNF antibodies determination	Electrophysiological assessment	Systemic adverse effects	Ocular adverse effects	Withdrawals due to inefficacy/adverse effects/other reasons
Androudi S, 2010	No	No	0	0	0/0/2 patients lost due to patients preferences, 1 patient lost to follow-up after 1st injection
Farvardin M, 2012		No	0	0	0/0/0
Haman RN, 2014		Yes	0	0	1 eye of a patient failed the treatment and was removed from the study due to worsening of inflammation and VA after the 4th injection/0/0
Markomichelakis N, 2012		No	0	0	0/0/0
Hamza MME, 2016		Yes	0	Subconjunctival hemorrhage in 4 patients after injection	0/0/0

Legend: TNF: tumor necrosis factor; VA: visual acuity

8. Illustrations and graphics

None.